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Original Contribution

Risk Factors for the Incidence of Endometrial Cancer according to the Aggressiveness of Disease

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There is a wide range of aggressiveness of endometrial tumors, some being indolent and easily treated while others metastasize and prove fatal. The authors used data from three population-based, case-control studies to determine if etiologic factors differ for aggressive disease. Interview data were obtained from 1,304 female residents of western Washington State who were 45–74 years of age and diagnosed with endometrial cancer during 1985–1991, 1994–1995, and 1997–1999 and from 1,779 controls who were of similar ages and selected primarily by random digit dialing. As a means of gauging aggressiveness, tumor characteristics were abstracted from the population-based cancer registry that serves western Washington State. The risk of endometrial cancer among long-term users ($\geq$8 years) of unopposed estrogens was particularly high for the least aggressive tumors (odds ratio = 18.6, 95% confidence interval: 12.2, 28.6) but was elevated for moderate and highly aggressive tumors as well (odds ratios = 6.6 and 7.1, respectively). Women who were obese, had a history of diabetes, and had fewer than two children were also at increased risk, regardless of tumor aggressiveness, while oral contraceptive users were at decreased risk of only relatively more aggressive disease. In general, a woman's risk of endometrial cancer appears to be influenced by similar risk factors regardless of disease severity.

endometrial neoplasms; neoplasm invasiveness

Abbreviations: CI, confidence interval; OR, odds ratio.

Endometrial cancer, the most common female gynecologic malignancy, is typically a curable disease. However, among the relatively small proportion of cases with advanced disease at the time of diagnosis, deaths from endometrial cancer are common. Reported 5-year survival for early stage disease averages 95 percent, whereas for advanced disease it ranges from 25 to 79 percent (1–6).

Prior studies of endometrial cancer in relation to the use of unopposed estrogens have observed an association with the incidence of advanced disease but not as strong an association as for less advanced disease (1, 2, 7–14). The size of the association between unopposed estrogen use and endometrial cancer may differ by histologic type. Endometrioid adenocarcinomas, which make up approximately 80 percent of all malignant endometrial tumors (15), have shown a stronger association with estrogen use than have histologic types characterized by a poorer prognosis (e.g., serous papillary, clear cell, and adenosquamous tumors)

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(4, 13, 15, 16). However, in any one study, there have been relatively small numbers of women with aggressive disease. Additionally, there has been little prior evaluation of other risk factors for endometrial cancer in relation to extent of disease (12, 17).

We analyzed data from several case-control studies to determine if known risk factors, notably use of unopposed estrogens and obesity, predispose to endometrial cancer to a different degree across the spectrum of disease severity.

MATERIALS AND METHODS

Study design

This study is composed of White (96 percent) and non-White women who participated in three population-based, case-control studies of endometrial cancer conducted in Washington State (18–22). The studies were approved by the Institutional Review Board of the Fred Hutchinson Cancer Research Center in Seattle, Washington.

The case group ($n = 1,304$) included women aged 45–74 years residing in King, Pierce, and Snohomish counties of western Washington State who were diagnosed with histologically confirmed endometrial cancer during 1985–1991, 1994–1995, and 1997–1999. All cases were identified through the Cancer Surveillance System, a population-based cancer registry affiliated with the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (23). Eligible case women had invasive epithelial tumors but not stage 0 (''in situ'') carcinoma of the endometrium. Of 1,738 eligible cases, 128 died before the interview, and another 304 declined to be interviewed (or their physician instructed the researchers not to contact them), for a response among cases of 75.1 percent. Of the 1,306 interviewed cases, one subject was excluded because of poor quality interview data, and one interview was lost.

The control women ($n = 1,779$) were ascertained using random digit dialing (24) and Health Care Financing Administration files. In order to enhance the likelihood of comparable ascertainment of exposures, controls were randomly assigned a referent date (the date prior to which exposure status was to be assessed) based on the distribution of diagnosis years for the cases. Control women aged 45–74 years for referent years 1985–1991 were identified through random digit dialing. Control women aged 50–65 years and 66–69 years for referent years 1994–1995 and 1997–1999 were identified through random digit dialing and also randomly selected from Health Care Financing Administration files, respectively. Eligible controls, with intact uteri and no prior history of endometrial cancer, were frequency matched to cases on 5-year age group and county of residence. Random digit dialing screening and interviews were successful in 94.5 percent and 77.2 percent of attempts, respectively, for an overall random digit dialing response of 73.0 percent (1,411 interviewed). Of 175 eligible Health Care Financing Administration controls, 116 (66.3 percent) agreed to an interview.

A subset of control women were obtained from a population-based, case-control study of breast cancer (the multicenter Contraceptive and Reproductive Experience (CARE) Study) (25). Participants were residents of King County who were aged 35–64 years and ascertained through random digit dialing. The screening response for these eligible controls was 83.6 percent, with 88.3 percent agreeing to an interview. The 252 controls aged 50–64 years with referent dates in 1994–1995 and 1997–1998 who had intact uteri and no previous history of endometrial cancer were included in our analyses.

Data collection

After informed consent, participants were interviewed using a structured, in-person questionnaire. All participants were asked questions about medication use, with specific attention to hormonal therapies, and about reproductive and medical history prior to diagnosis or referent date. Detailed information was collected on type of postmenopausal hormone therapy. Photographs of common medications and a life-events calendar were used to aid in recall. Respondents interviewed by telephone (37 cases and 60 controls) received photographs of hormonal preparations by mail before the interview. The reliability and validity of the methods used to ascertain hormone therapy have been previously documented (26–29).

Classification of cancer aggressiveness

Information on tumor grade and extent of disease at the time of diagnosis was taken from the records of the Cancer Surveillance System. Endometrial tumors were classified into three severity groups according to the scheme outlined in *Novak's Gynecology* (30): 1) low (grade 1 or 2 lesions that were confined to the endometrium); 2) moderate (grade 3 lesions that were confined to the endometrium or grade 1–3 lesions that either invaded the myometrium or extended to the isthmus/cervix); and 3) high (grade 4 lesions or grade 1–3 lesions that spread beyond the myometrium).

Classification of postmenopausal hormone use

Women were categorized as users of postmenopausal hormones if they took this therapy for at least 6 months. A separate analysis was performed for each type of hormone regimen: 1) unopposed estrogen; 2) estrogens opposed by progestogen for <10 days per month; 3) estrogens opposed by progestogen for 10–24 days per month; and 4) continuous combined estrogen and progestogen (progestogen for >24 days per month). Women who used more than one of these hormone preparations for more than 6 months were excluded from analyses.

To control for potential confounding when examining the possible influence of other exposures or characteristics on the risk of endometrial cancer, we classified postmenopausal hormone use into three categories by duration and recency of use of unopposed estrogens and estrogens plus progestogen. The categories were defined by the case-control differences observed as 1) low risk (no hormone use or <6 months of unopposed estrogen or estrogen plus progestogen for <10 days per month); 2) intermediate risk (unopposed estrogen for 6 months–4 years regardless of recency, unopposed estrogen for >4–8 years and quit >2 years prior to the referent

date, or estrogen plus progestogen (progestogen for <10 days per month) for <12 years regardless of recency); and 3) high risk (unopposed estrogen for >4–8 years and quit <2 years prior to the referent date, unopposed estrogen for >8 years regardless of recency, or estrogen plus progestogen (progestogen for <10 days per month) for >12 years regardless of recency). Women who were users of estrogen plus progestogen for 10–24 days per month or as continuous combined therapy are classified as nonusers (of unopposed estrogen or estrogen plus progestogen for <10 days per month).

Unlike for the exposure variable, the variable created for control of confounding does not exclude women who used more than one hormone preparation. If a woman used unopposed estrogen in the medium-risk category but also used estrogen plus progestogen (progestogen for <10 days per month) in the high-risk group, then the high-risk rating takes precedence. Similarly, if a woman used estrogen plus progestogen (progestogen for <10 days per month) in the medium-risk category but also used unopposed estrogen in the high-risk group, then the high-risk rating takes precedence.

Statistical analysis

Polytomous logistic regression was used to compute odds ratios, which closely estimate relative risks in studies of low-incidence conditions, and associated 95 percent confidence intervals for each of the main exposure variables and endometrial cancer and to evaluate possible confounding of this relation by other factors. Frequency matching variables (age at referent date, county of residence, and referent year) and factors that altered the odds ratio by at least 10 percent were included in the final multivariate models. To test for the homogeneity of odds ratios across categories of tumor aggressiveness by levels of each exposure variable, we compared constrained regression models using the likelihood ratio test. All analyses were performed using the STATA statistical package, version 8 (Stata Corporation, College Station, Texas).

RESULTS

For 23 women there was insufficient information on their tumor's grade, extent of disease, or metastases to reliably categorize the severity of the malignancy. The remainder were categorized as having low ($n = 500$), moderate ($n = 650$), or high ($n = 131$) aggression disease. As has been observed for numerous other study populations (for reviews, refer to references 31 and 32), the mean body mass index of cases was higher than that of controls. Relative to controls, cases also tended to have fewer children and were more likely to have a history of diabetes or hypertension. A higher proportion of cases had been users of postmenopausal estrogens, whereas a higher proportion of controls had used oral contraceptives or had smoked cigarettes. Almost 90 percent of the histologic subtypes associated with relatively high mortality (e.g., clear cell, adenosquamous, papillary serous) were observed in the moderate and high aggression cases.

The risk of low, moderate, and high aggressive endometrial cancer in relation to prior hormone use is presented in table 1. For all levels of severity, risk rose steadily with increasing duration of use of unopposed estrogens. The risk among long-term users (≥8 years) of unopposed estrogens, relative to women who had never received any menopausal hormone therapy, was particularly high for the least aggressive form of endometrial cancer (odds ratio (OR) = 18.6, 95 percent confidence interval (CI): 12.2, 28.6). The corresponding odds ratios for moderate and high aggression tumors were elevated as well: 9.8 (95 percent CI: 6.6, 14.7) and 7.1 (95 percent CI: 3.6, 14.2), respectively. The risk among women who used estrogens opposed by progestogens for fewer than 10 days per month for 4 or more years was also particularly high for the least aggressive form of endometrial cancer (OR = 6.2, 95 percent CI: 3.2, 12.0), and there was at least a suggestion that the corresponding odds ratios for tumors of moderate and high aggressiveness were elevated as well (OR = 3.1, 95 percent CI: 1.6, 6.1 and OR = 1.6, 95 percent CI: 0.4, 7.2, respectively). Use of estrogens opposed by progestogen 10–24 days per month for 4 or more years was associated with an increased risk of tumors of low aggressiveness (OR = 2.9, 95 percent CI: 1.6, 5.0) but not of the more serious forms of endometrial cancer. Use of continuous combined hormone therapy, while associated with a reduced risk of mild disease, bore no apparent relation to the incidence of aggressive endometrial cancer.

Among women whose body mass index was between 30.0 and 34.9 kg/m^2, the risk of endometrial cancer was increased to a similar degree irrespective of tumor aggressiveness (ORs = 1.6–1.7) (table 2). Among women with a body mass index of 35.0 or more kg/m^2, the risk rose to 5.1 (95 percent CI: 3.5, 7.4), 5.1 (95 percent CI: 3.7, 7.1), and 4.0 (95 percent CI: 2.2, 7.1) for cancers of low, moderate, and high severity, respectively.

A history of diabetes was modestly associated with an increased risk of endometrial cancer across the spectrum of disease severity (ORs = 1.2–1.9) (table 3). The odds ratio for highly aggressive tumors was 1.6 (95 percent CI: 0.8, 3.1). A history of hypertension was associated with at most a small increase in the risk of disease for cancers of low (OR = 1.2, 95 percent CI: 1.0, 1.6), moderate (OR = 1.1, 95 percent CI: 0.9, 1.4), and high (OR = 1.1, 95 percent CI: 0.7, 1.6) degree of aggression. Women who gave birth to two or more children were at a 30–60 percent reduced risk across the spectrum of disease (table 3). Ever use of oral contraceptives was negatively associated with disease of moderate and high aggressiveness (OR = 0.7, 95 percent CI: 0.6, 0.9 and OR = 0.6, 95 percent CI: 0.4, 0.9, respectively) but not low aggressiveness (table 3). Former smoking was associated with a 30–60 percent reduction in risk of endometrial cancer across the spectrum of disease. Current smoking, on the other hand, though negatively associated with milder forms of endometrial cancer, was unrelated to the incidence of aggressive disease (table 3).

DISCUSSION

In terms of ischemic heart disease and breast cancer, there are reasons to believe that only postmenopausal hormone regimens that include a progestogen increase a woman's risk (33–35). Long-term use of hormone regimens that do not

TABLE 1. Association between postmenopausal estrogen use and risk of endometrial cancer, by tumor aggressiveness, Washington State, 1985–1987, 1988–1991, 1994–1995, and 1997–1999*

	Controls ($n = 1,779$) (no. (%))	Low tumor aggressiveness ($n = 500$)			Moderate tumor aggressiveness ($n = 650$)			High tumor aggressiveness ($n = 131$)			p value†
		No. (%)	Odds ratio‡	95% confidence interval	No. (%)	Odds ratio‡	95% confidence interval	No. (%)	Odds ratio‡	95% confidence interval	
Use of unopposed estrogen											
Nonuser	1,058 (84.8)	196 (53.8)	1.0	Referent	323 (65.8)	1.0	Referent	65 (67.0)	1.0	Referent	
6 months–3.9 years	103 (8.3)	41 (11.3)	2.6	1.7, 3.9	46 (9.4)	1.8	1.2, 2.7	13 (13.4)	2.4	1.2, 4.7	0.15
4.0–7.9 years	39 (3.1)	27 (7.4)	4.9	2.8, 8.5	22 (4.5)	2.5	1.4, 4.4	4 (4.1)	2.2	0.7, 6.5	0.04
≥8 years	48 (3.8)	100 (27.5)	18.6	12.2, 28.6	100 (20.7)	9.8	6.6, 14.7	15 (15.5)	7.1	3.6, 14.2	<0.01
Use of sequential estrogen plus progestogen											
<10 days/month											
Nonuser	1,058 (95.8)	196 (88.3)	1.0	Referent	323 (93.6)	1.0	Referent	65 (92.9)	1.0	Referent	
6 months–3.9 years	19 (1.7)	8 (3.6)	2.6	1.1, 6.4	7 (2.0)	1.8	0.7, 4.7	3 (4.3)	3.4	1.0, 12.2	0.52
≥4.0 years	27 (2.4)	18 (8.1)	6.2	3.2, 12.0	15 (4.3)	3.1	1.6, 6.1	2 (2.9)	1.6	0.4, 7.2	0.07
10–24 days/month											
Nonuser	1,058 (88.4)	196 (87.5)	1.0	Referent	323 (91.8)	1.0	Referent	65 (92.9)	1.0	Referent	
6 months–3.9 years	73 (6.1)	7 (3.1)	0.7	0.3, 1.5	11 (3.1)	0.7	0.4, 1.4	2 (2.9)	0.6	0.1, 2.3	0.93
≥4.0 years	66 (5.5)	21 (9.4)	2.9	1.6, 5.0	18 (5.1)	1.4	0.8, 2.5	3 (4.3)	1.0	0.3, 3.4	0.05
Use of continuous combined estrogen plus progestogen											
Nonuser	1,058 (88.2)	196 (94.7)	1.0	Referent	323 (91.5)	1.0	Referent	65 (83.3)	1.0	Referent	
6 months–3.9 years	66 (5.5)	4 (1.9)	0.4	0.1, 1.1	10 (2.8)	0.5	0.2, 1.0	4 (5.1)	0.9	0.3, 2.7	0.69
≥4.0 years	76 (6.3)	7 (3.4)	0.7	0.3, 1.7	20 (5.7)	1.0	0.6, 1.7	9 (11.5)	1.6	0.7, 3.8	0.53

* Excludes women who were users of other hormones; 55 subjects (37 controls, 18 cases) were missing information on hormone use.
† Test for homogeneity of odds ratios across case groups defined by tumor aggressiveness.
‡ Odds ratios adjusted for body mass index (<18.5, 18.5–24.9, 25.0–29.9, 30.0–34.9, ≥35); age (45–54, 55–64, 65–74 years); county of residence (King, Pierce, Snohomish); and referent year (1985–1987, 1988–1991, 1994–1995, 1997–1999).

include a progestogen sharply increase the incidence of endometrial cancer, particularly for tumors that carry a good prognosis (1, 7–11, 13, 21, 36–39). To the extent that there may be an increase in women's use of regimens with low or absent progestogen content in an effort to minimize risk of ischemic heart disease and breast cancer, the magnitude of the increased risk of more serious endometrial tumors associated with such regimens becomes important.

Prior studies of postmenopausal hormone therapy in relation to risk of endometrial cancer have observed the strongest

TABLE 2. Association between body mass index and risk of endometrial cancer, by tumor aggressiveness, Washington State, 1985–1987, 1988–1991, 1994–1995, and 1997–1999

Body mass index*	Controls ($n = 1,779$) (no. (%))	Low tumor aggressiveness ($n = 500$)			Moderate tumor aggressiveness ($n = 650$)			High tumor aggressiveness ($n = 131$)			p value†
		No. (%)	Odds ratio‡	95% confidence interval	No. (%)	Odds ratio‡	95% confidence interval	No. (%)	Odds ratio‡	95% confidence interval	
<30.0 kg/m^2	1,508 (85.0)	374 (75.4)	1.0	Referent	448 (69.2)	1.0	Referent	93 (71.0)	1.0	Referent	
30.0–34.9 kg/m^2	181 (10.2)	57 (11.5)	1.6	1.2, 2.3	90 (13.9)	1.6	1.2, 2.2	18 (13.7)	1.7	1.0, 2.9	0.90
≥35.0 kg/m^2	85 (4.8)	65 (13.1)	5.1	3.5, 7.4	109 (16.8)	5.1	3.7, 7.1	20 (15.3)	4.0	2.2, 7.1	0.95

* Missing information on body mass index were 12 subjects (five controls, seven cases).
† Test for homogeneity of odds ratios across case groups defined by tumor aggressiveness.
‡ Odds ratios adjusted for postmenopausal hormone use (low, intermediate, high risk); age (45–54, 55–64, 65–74 years); county of residence (King, Pierce, Snohomish); referent year (1985–1987, 1988–1991, 1994–1995, 1997–1999).

TABLE 3. Association between other risk factors and incidence of endometrial cancer, by tumor aggressiveness, Washington State, 1985–1987, 1988–1991, 1994–1995, and 1997–1999

	Controls ($n = 1,779$) (no. (%))	Low tumor aggressiveness ($n = 500$)			Moderate tumor aggressiveness ($n = 650$)			High tumor aggressiveness ($n = 131$)			p value*
		No. (%)	Odds ratio†	95% confidence interval	No. (%)	Odds ratio†	95% confidence interval	No. (%)	Odds ratio†	95% confidence interval	
History of diabetes‡											
No	1,704 (95.8)	468 (93.6)	1.0	Referent	580 (89.2)	1.0	Referent	118 (90.1)	1.0	Referent	
Yes	75 (4.2)	32 (6.4)	1.2	0.8, 2.0	70 (10.8)	1.9	1.3, 2.8	13 (9.9)	1.6	0.8, 3.1	0.10
History of hypertension‡											
No	1,297 (73.0)	314 (62.9)	1.0	Referent	411 (63.3)	1.0	Referent	86 (65.6)	1.0	Referent	
Yes	479 (27.0)	185 (37.1)	1.2	1.0, 1.6	238 (36.7)	1.1	0.9, 1.4	45 (34.4)	1.1	0.7, 1.6	0.55
Parity (no. of livebirths)											
0	189 (10.6)	78 (15.6)	1.0	Referent	114 (17.5)	1.0	Referent	26 (19.8)	1.0	Referent	
1	184 (10.3)	61 (12.2)	0.8	0.5, 1.2	81 (12.9)	0.7	0.5, 1.1	17 (13.0)	0.6	0.3, 1.2	0.71
≥2	1,406 (79.0)	361 (72.2)	0.7	0.5, 0.9	452 (69.5)	0.5	0.4, 0.7	88 (67.2)	0.4	0.3, 0.7	0.15
Ever use of oral contraceptives											
No	883 (50.4)	269 (54.0)	1.0	Referent	411 (63.4)	1.0	Referent	84 (64.1)	1.0	Referent	
Yes	869 (49.6)	229 (46.0)	1.2	0.9, 1.5	237 (36.6)	0.7	0.6, 0.9	47 (35.9)	0.6	0.4, 0.9	<0.01
Smoking status											
Never	789 (44.4)	266 (53.3)	1.0	Referent	377 (58.0)	1.0	Referent	75 (57.3)	1.0	Referent	
Former	624 (35.1)	148 (29.7)	0.7	0.5, 0.8	198 (30.5)	0.6	0.5, 0.8	27 (20.6)	0.4	0.3, 0.7	0.56
Current	366 (20.6)	85 (17.0)	0.7	0.5, 0.9	75 (11.5)	0.5	0.4, 0.6	29 (22.1)	1.0	0.6, 1.5	0.07

* Test for homogeneity of odds ratios across case groups defined by tumor aggressiveness.

† Odds ratios adjusted for postmenopausal hormone use (low, intermediate, high risk); body mass index (<18.5, 18.5–24.9, 25.0–29.9, 30.0–34.9, ≥35); age (45–54, 55–64, 65–74 years); county of residence (King, Pierce, Snohomish); and referent year (1985–1987, 1988–1991, 1994–1995, 1997–1999).

‡ Medically treated diabetes or hypertension.

associations with the least aggressive tumors (1, 2, 7–14). Our observation of a 19-fold increased risk of less aggressive disease with long-term use of unopposed estrogens was consistent with the published literature. However, such use was nonetheless associated with a 10-fold and a sevenfold increased risk, respectively, of the incidence of moderate and high aggression tumors.

In our study, obesity, diabetes, and parity of two or more were associated with aggressive endometrial tumors to nearly the same degree as they were with more indolent tumors at this site. Obesity-related risk has been reported to be highest for the least aggressive tumors in a study by La Vecchia et al. (12), but the study was modest in size and the odds ratios were above 1.0 regardless of severity. A more recent study observed no difference in risk associated with weight by stage or grade of tumor (17).

With respect to parity, one previous study observed no difference in risk by tumor aggressiveness (17). In another study, parity was associated with decreased risk of low aggression (endometrioid) tumors but not high aggression (serous) tumors (16), but there were only 26 cases in the latter category. The negative associations between cigarette smoking and use of oral contraceptives and risk of endometrial cancer have not been observed in prior studies to differ by tumor aggressiveness (16, 17).

Serous, clear cell, squamous, and undifferentiated endometrial tumors are most frequently aggressive and have a poor prognosis, with 5-year survival ranging from 30 to 70 percent (3, 40–44). In the early 1980s, attention was called specifically to uterine serous papillary carcinomas, whose aggressive nature frequently led to spread outside of the endometrium (5, 43, 45–49). While unopposed estrogen users have an increased risk of aggressive tumors, it has not been clear whether they specifically have an elevated risk of these unfavorable histopathologic subtypes (16, 17). Because of the small number of uterine serous papillary carcinomas ($n = 20$), we did not explore these relations.

There are some limitations to the current study. The first concerns the evaluation of disease aggressiveness, which was 1) restricted to the time of diagnosis and 2) not standardized across institutions (i.e., no central review). As is true of most studies, self-report of exposure status on which we relied undoubtedly was inaccurate in some instances. Only 54 percent of eligible women with advanced disease were willing or able to provide interview information (although interviewed and noninterviewed cases with advanced

disease were similar with respect to the demographic characteristics available in the cancer registry data). Finally, the relatively small number of aggressive cases that we were able to include ($n = 131$) led to some statistically imprecise estimates of associations with less common exposures (e.g., current cigarette smoking).

Aggressive endometrial malignancies are not as common as less aggressive tumors, but this study and earlier studies suggest that, in large part, their incidence is influenced by the same factors.

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